COMMONWEALTH OF AUSTRALIA
Statutory Declarations Act 1959

IN THE MATTER of United States Patent Application No. 10/019,816 in the name of **Michael Valentine Agrez** and **Nuhzat Ahmed**

STATUTORY DECLARATION

I, Michael Valentine Agrez, of 46 Sherburn Place, Charlestown, NSW 2290, Australia, do sincerely declare as follows.

1. I am an Associate Professor of the University of Newcastle, NSW, Australia and an inventor of the invention in respect of which United States Patent Application No. 10/019,816 (the "**Application**") has been filed.

2. The major thrust of my research during the past 20 years has been directed at growth signaling in colon cancer cells. After graduating in medicine and then specializing in colorectal surgery (MB.BS, FRCS, FRACS) my two subsequent doctoral theses were in the fields of cancer cell biology (MS) and molecular cell biology (PhD). In recognition of my research achievements as a scientist in parallel with a clinical career, I was awarded the John Mitchell Crouch Fellowship in the year 2000 – the highest award offered by the Royal Australasian College of Surgeons to one individual in Australia each year. Scientific articles dealing specifically with biochemical, molecular or cellular aspects of cancer number more than 30 and have been published in high ranking international peer-reviewed journals such as Journal of Cell Biology, Journal of Biological Chemistry, Oncogene, International Journal of Cancer, British Journal of Cancer, European Journal of Cancer, Virology, Journal of Virology, Molecular Biology of the Cell, Journal of Surgical Oncology and Biochemical Biophysical Research Communications amongst others.

3. I have reviewed the Official Action dated 2 December 2005 issued by the United States Patent & Trade Mark Office (**USPTO**) in respect of the Application. I understand the United States Examiner has suggested that stability, release and manufacturing challenges must be met in order to address technical difficulties associated with the delivery of proteins *in vivo*. In support of this, the Examiner has made reference to Johns and Tracey "Peptide and Protein Drug Delivery", In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833.

4. I understand the United States Examiner has further suggested the specification for the Application does not teach means for the delivery of polypeptide agents to the appropriate site and the efficacious uptake by tumours to obtain inhibition of cancer cells in a patient, and it would be undue experimentation for a person in my field of technology to treat patients with peptide agents as described in the Application.

5. Results of experiments that I have conducted or which have been conducted under my supervision or pursuant to my request, clearly show that efficacious *in vivo* treatment of cancer cells utilising peptide agents described in the Application can be readily obtained without the need for any special formulations or means for stabilizing the peptides.

6. The results for some of these experiments are set out in Annexure **MVA-1** attached to this declaration. In particular, a number of graphs (**Graphs A-F**) are presented showing a number of different peptides described in the Application administered to Balb/c nude mice by different routes in the treatment of a number of different cancers.

7. Specifically, Graphs A and B show that the administration of the peptide AAVALLPAVLLALLARSKAKWQTGTNPLYR (**IK1**) comprising the binding domain of the β6 integrin subunit for the MAP kinase Erk2 administered intraperitoneally (Graph A) or intratumourally (4.3 mg/kg) (Graph B) in standard Dulbecco's Modified Eagle's Medium (**DMEM**) inhibited the growth of human HT29 colon cancer xenografts compared to DMEM alone.

8. Graph C shows that administration of the peptide AAVALLPAVLLALLAP RSKAKNPLYR (**IK2P**) intravenously (**IV**) twice weekly in standard DMEM inhibited the growth of HT29 human colon cancer xenografts compared to DMEM alone. This experiment further showed the peptide was well tolerated.

9. Graph D shows that administration of the peptide AAVALLPAVLLALLARSKAKNPLYR (**IK2**) at 6 mg/kg or 12 mg/kg daily for 7 days via subcutaneous injection in normal saline is more effective at inhibiting growth of human HT29 colon cancer xenografts than IK1 in normal saline or normal saline alone.

10. Graph E shows that IK2 administered via subcutaneous injection daily for 7 days at 12 mg/kg in normal saline inhibited the growth of HL60 human leukaemic cell xenografts compared to normal saline alone.

11. Graph F shows that the peptide AAVALLPAVLLALLARARAKNPLYK (**IK3**) comprising the binding domain of the β3 integrin subunit for the MAP kinase Erk2 administered via subcutaneous injection daily over a period of 5 days at 12 mg/kg in normal saline inhibited the growth of DU145 human prostate xenografts compared to normal saline alone.

12. The specification for the Application describes several well known methods for transporting active peptide agents into cells including the use of the transport peptide penetratin. The use of signal peptides such as AAVALLPAVLLALLAP to transport peptide agents into cells has previously been described, see for instance US Patent 5,807,746 (Lin et al).

13. The active peptides RSKAKWQTGTNPLYR, RSKAKNPLYR and RARAKNPLYK are described in the specification for the Application at, for instance, page 49, line 23 to page 50, line 2, and page 92, line 6. DMEM and normal saline are commonly used for administration of peptide agents. I also believe that the dosages of the active peptides used to obtain the results shown in Annexure MVA-1 are in normal ranges that any person in my field would as a matter of routine employ for administration of peptide agents.

I understand that a person who intentionally makes a false statement in a statutory declaration is guilty of an offence under section 11 of the Statutory Declarations Act 1959, and I believe that the statements contained in this declaration are true in every particular.

DECLARED at Newcastle, Australia on the 15th of August 2006.

Before me: _____

_____ _____

Witness – Print full name and status Michael Valentine Agrez

REGISTERED PATENT ATTORNEY

THIS IS ANNEXURE MVA-1

to

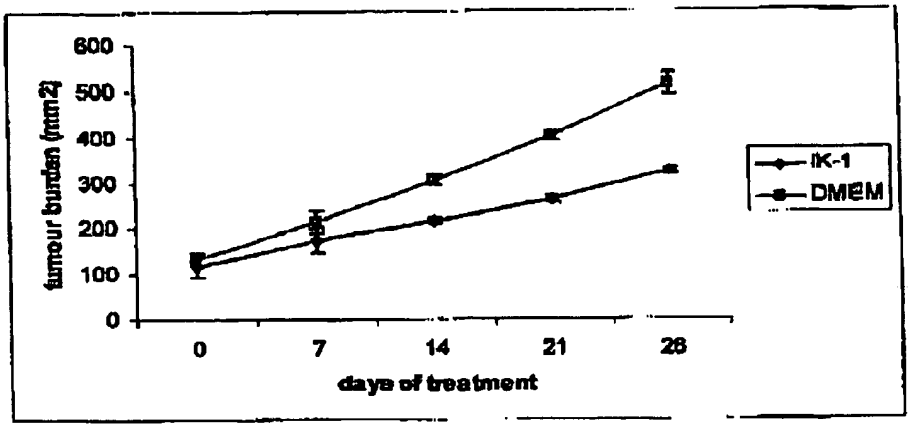
THE STATUTORY DECLARATION

of

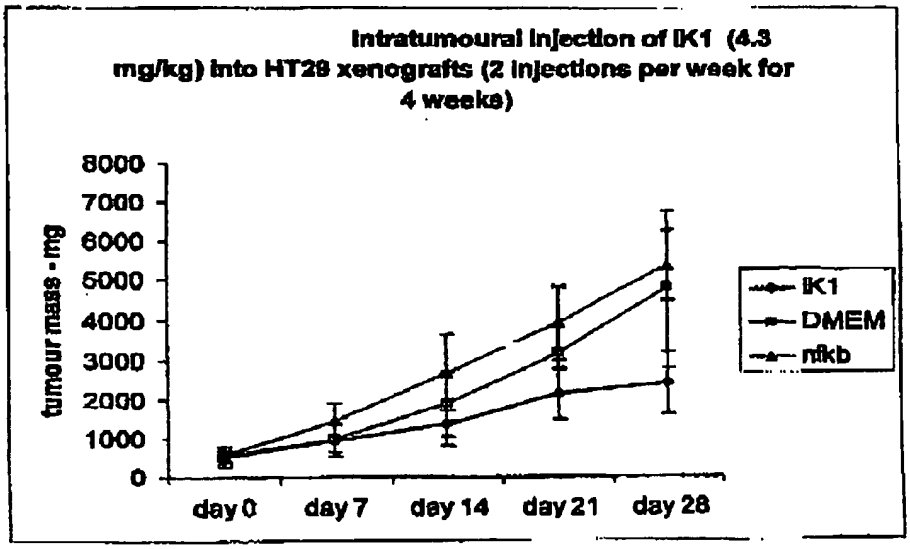
MICHAEL VALENTINE AGREZ

DATED the 15th day of August 2006

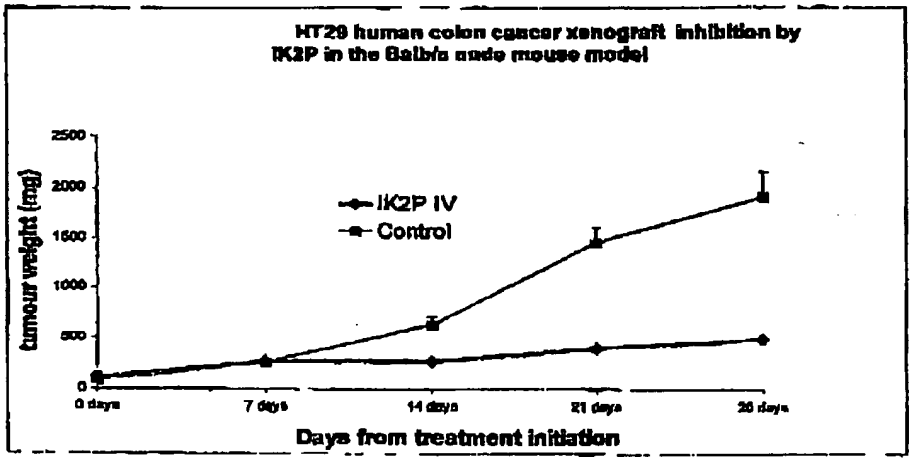
Witness - Signature



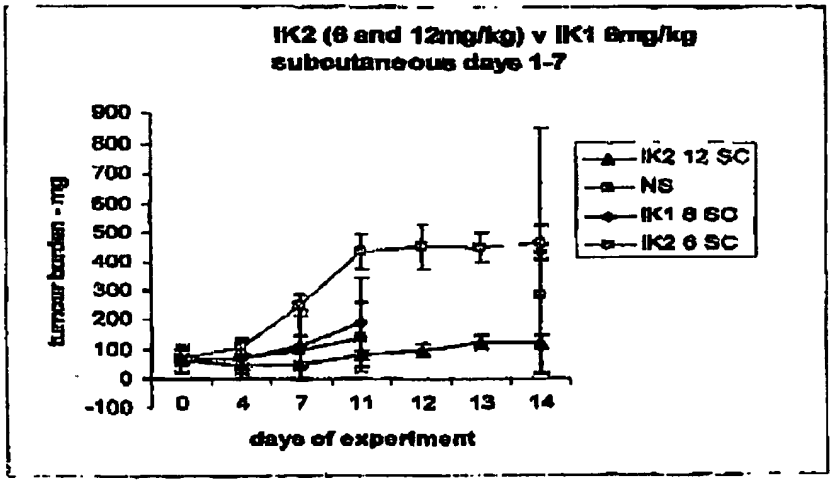
GRAPH A



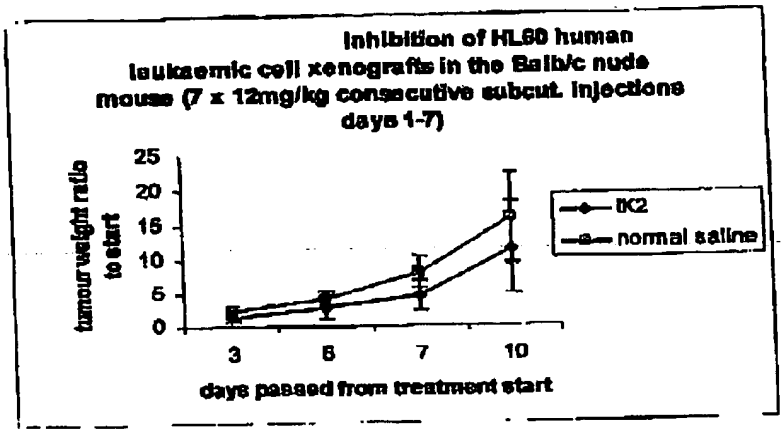
GRAPH B



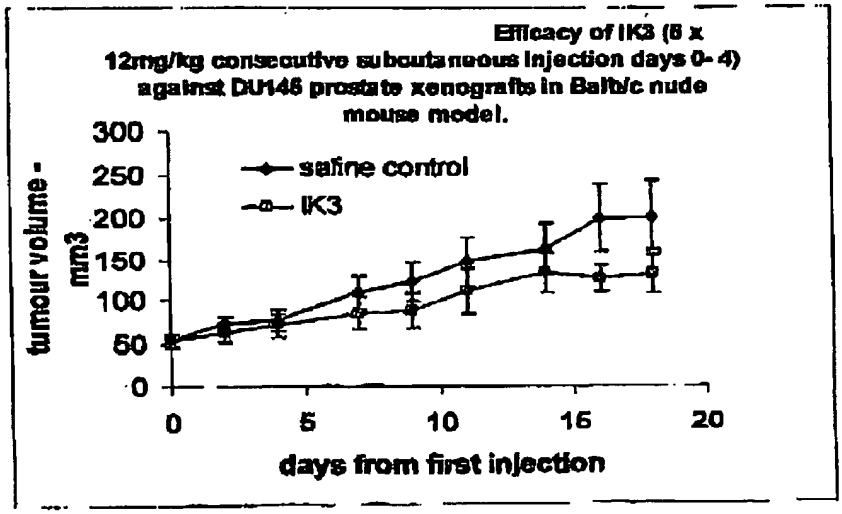
GRAPH C



GRAPH D



GRAPH E



GRAPH F